Chemical: 1,4-Dioxane
CAS No.: 123-91-1 Preparation Date: 01/26/88

A. U.S. EPA CLASSIFICATION AND BASIS

Classification: B2, probable human carcinogen, based on induction of nasal cavity and liver carcinomas in multiple strains of rats, liver carcinomas in mice, and gall bladder carcinomas in guinea pigs.

1. HUMAN DATA

Inadequate. Three epidemiologic studies on workers exposed to 1,4-dioxane are available. Theiss et al. (1976) reported on 12 deaths among 74 workers exposed to dioxane. Two of the deaths were due to cancer, one lamellar epithelial carcinoma in a 66-year-old man and one myelofibrotic leukemia in a 71-year-old man. No statistically significant increase was noted based on these few cases of cancer. Among 165 production and processing workers exposed to dioxane (as well as vinyl chloride, trichloroethylene, and carbon tetrachloride), 12 deaths were reported (Buffler et al., 1976). Three of these deaths were due to cancer: one stomach cancer, one alveolar carcinoma, and one mediastinal malignancy. These deaths were not different from the expected numbers. In an unpublished report to NIOSH by Dernehl (1976), four cancers were reported among 80 dioxane workers. The cancers included a colonic cancer, a pulmonary cancer, a lymphosarcoma, and a glioblastoma. Again, the observed number of cancer cases was not different from the expected cancer deaths.

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2. ANIMAL DATA

SIGNIFICANTLY ELEVATED

Sufficient. The NCI (1978) administered 1,4-dioxane (greater than or equal to 99.9% pure) in the drinking water to Osborne-Mendel rats and mice for a significant portion of their lifespan (110 weeks, rats; 90 weeks, mice). Male and female rats were given 530, 240, or 0 mg/kg/day and 640, 350, or 0 mg/kg/day, respectively. High-dose and matched control male rats were placed in the study 1 year after the study began to replace two original groups of male rats that had died during an air-conditioning failure. Male and female treated rats had a incidence of nasal cavity and treated female rats had an elevated incidence of liver adenomas. Male and female mice treated with 830, 720, or 0 mg/kg/day and 860, 380, or 0 mg/kg/day, respectively, developed an elevated incidence of liver carcinomas and liver carcinomas or adenomas, both dose-related. Survival rate of treated rats and female mice were decreased by comparison to controls, but the NCI concluded that sufficient numbers of animals were at risk of developing tumors.

Kociba et al. (1974) administered 1%, 0.1%, 0.01%, or 0% 1,4-dioxane in the drinking water to male and female Sherman rats (60 rats/sex/treatment group). After 24 months, the incidences of hepatocellular carcinomas, liver cholangiomas, and nasal cavity squamous cell carcinomas were increased in the high-dose rats. Similar administration of 0.5% to 2% 1,4-dioxane to male guinea pigs for 23 months induced gall bladder carcinomas (2/22) and liver hepatomas (3/22) (Hogh-Ligeti and Argus, 1970). Hogh-Ligeti et al. (1970) and Argus et al. (1973) treated male Sprague-Dawley rats with 1.8, 1.4, 1.0, 0.75, or 0% 1,4-dioxane in the drinking water for 13 months, followed by a 3-month observation period. Treatment-related hepatocellular carcinomas and nasal cavity carcinomas were observed at 1.8% and 1.4%-dioxane, and treatment-related nasal cavity carcinomas were observed at 1.0% and 0.75% 1,4-dioxane. Liver tumors (7/26) were induced in male Wistar rats after oral administration of 1% 1,4-dioxane in the drinking water for 63 weeks (Argus et al., 1965). One kidney carcinoma and one myeloid leukemia were also observed in the treated animals. One lymphoid tissue lymphosarcoma was observed in the 9 control rats.

In a 2-year inhalation study, male and female Wistar rats were exposed to 111 ppm or 0 ppm 1,4-dioxane vapor. Three replicate groups of 288 rats/sex served as the treated and control groups (Torkelson et al., 1974). Comprehensive gross and microscopic examination of the major organs and tissues revealed no treatment-related lesions.

1,4-Dioxane was found to be a promoter in a two-stage skin carcinogenesis study in mice (King et al., 1973). A single dermal application of 50 µg of 7,12-dimethylbenzo-anthracene (DMBA) was followed one week later by thrice-weekly paintings of 1,4-dioxane (unspecified concentration in acetone) for 60 weeks Similar applications of 1,4-dioxane without DMBA initiation did not result in a significantly increased incidence of skin tumors.

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3. SUPPORTING DATA

B. ORAL QUANTITATIVE ESTIMATE

Slope Factor = 1E-2/mg/kg/day

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1. UNIT RISK SUMMARY TABLE

Water Concentrations Producing Risk Levels E-4	E-5	E-6	Unit Risk (/ug/L)	Model
3E+2	3E+1	3	3E-7	linearized multistage (extra risk)

2. DOSE-RESPONSE DATA

Species/Strain Tumor Type	Dose Administered	Human Equivalent	Tumor Incidence	Reference
Rat/Osborne-Mendel, male, squamous cell carcinoma of the nasal turbinates	Route: oral, drinking water			NCI, 1978
	%	mg/kg/day		
	0	0	0/33	
	0.5	240	12/25	
	1.0	530	16/33	

3. ADDITIONAL COMMENTS

Transformed doses in mg/kg/day were provided by the study author. NCI (1978) determined average daily doses from the mean consumption of dioxane solution per week at intervals during the second year of treatment. The length of exposure and experiment was 770 and 819 days for treated and control animals, respectively.

The unit risk should be used if the water concentration exceeds 3E+4 ug/L, since above this concentration the slope factor may differ from that stated.

4. STATEMENT OF CONFIDENCE IN THE ORAL QUANTITATIVE ESTIMATE

The compound was administered at multiple dose levels by a natural route of exposure. The animals were exposed for a significant portion of their lifespan, and comprehensive histologic examinations were performed. Although survival was affected by treatment, adequate numbers of rats were at risk for development of late-appearing tumors.

C. INHALATION QUANTITATIVE ESTIMATE

Not available.

D. DOCUMENTATION AND REVIEW

1. REFERENCES

U.S. EPA. 1986. Reportable Quantities Document for 1,4-Dioxane (review draft). Prepared by the Carcinogen Assessment Group, Office of Health and Environmental Assessment, Washington, D.C. for the Office of Emergency and Remedial Response and Office of Solid Waste and Emergency Response, Cincinnati, OH.

National Cancer Insitute (NCI). 1978. Bioassay of 1,4-Dioxane for Possible Carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 80. DHEW Publication No. (NIH) PB-285-711.

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2. REVIEW

The values in the 1986 Reportable Quantities Document for 1,4-dioxane have received limited Agency review.

Agency Work Group Review: 05/13/87, 02/03/88

Verification Date: __/__/__

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3. U.S. EPA CONTACTS

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